

Remarks

The Amendments

Claims 1, 3, 14-21, 30 and 35 are pending. With the present submission, new claims 36-39 have been added.

Independent claim 1 has been amended to recite "A chemically modified nucleic acid molecule, wherein: a) the nucleic acid molecule comprises a sense strand and a separate antisense strand, each strand having one or more pyrimidine nucleotides and one or more purine nucleotides; b) each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in length; c) an 18 to 27 nucleotide sequence of the antisense strand of the nucleic acid molecule is complementary to a human amyloid precursor protein (APP) RNA sequence encoded by SEQ ID NO: 1905; d) an 18 to 27 nucleotide sequence of the sense strand of the nucleic acid is complementary to the antisense strand and comprises an 18 to 27 nucleotide sequence of the human APP RNA sequence; e) about 50 to 100 percent of the nucleotides in the sense strand and about 50 to 100 percent of the nucleotides in the strand are chemically modified with modifications independently selected from the group consisting of 2'-O-methyl, 2'-deoxy-2'-fluoro, 2'-deoxy, phosphorothioate and deoxyabasic modifications; and f) one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides." Support for the amendment can be found at, *inter alia*, page 15, lines 20-30; page 18, lines 26-27; page 24, lines 15-32; page 25, lines 1-15; page 36, lines 1-10; page 71, lines 16-31; page 77, lines 21-27; page 81, lines 8-10; page 153; Figures 4-5; and Tables III and IV; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 12; lines 1-15, and page 425); 60/409,293 (*see, e.g.*, page 35, lines 9-29; page 19, lines 20-29; and page 20, lines 1-10); 60/440,129 (*see, e.g.*, page 12, lines 1-20); and 60/358,580 (*see, e.g.*, page 3, lines 16-19; page 5, lines 13-16; page 8, lines 9-18; page 10, lines 7-12; and page 11, lines 27-30).

Support for amended claim 3 can be found at, *inter alia*, page 18, lines 26-27; page 81, lines 8-10; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application No. 60/358,580 (*see, e.g.*, page 5, lines 1-4, and page 23, lines 5-7).

Support for amended claim 14 can be found at, *inter alia*, page 15, lines 8-30; page 19, lines 24-27, and 30-32; page 24, lines 15-32; page 25, lines 1-15; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application No. 60/440,129 (*see, e.g.*, page 22, lines 1-9, and page 10, lines 13-17).

Support for amended claim 15 can be found at, *inter alia*, page 15, lines 8-30; page 19, lines 30-32; page 24, lines 15-32; page 25, lines 1-15, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 3-16, and page 11, lines 1-11); 60/440,129 (*see, e.g.*, page 15, lines 14-20, and page 10, lines 10-13); and 60/358,580 (*see, e.g.*, page 10, lines 7-10).

Support for amended claim 16 can be found at, *inter alia*, page 15, lines 20-30; page 20, lines 6-14; page 24, lines 15-32; page 25, lines 1-15; page 33, lines 12-18; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 3-16, and page 11, lines 1-11); 60/440,129 (*see, e.g.*, page 16, lines 19-25, and page 21); and 60/358,580 (*see, e.g.*, page 10, lines 2-3, and 7-12, and page 35, lines 1-15).

Support for amended claim 17 can be found at, *inter alia*, page 15, lines 20-30; page 24, lines 15-32; page 25, lines 1-15; page 46, lines 18-20; page 68, lines 5-7; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 40, lines 4-18); 60/440,129 (*see, e.g.*, page 20, lines 1-5); and 60/358,580 (*see, e.g.*, page 35, lines 5-7).

Support for amended claim 18 can be found at, *inter alia*, page 15, lines 8-30; page 19, line 32, to page 20, line 2; page 24, lines 15-32; page 25, lines 1-15, and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 3-16, and page 11, lines 1-11); 60/440,129 (*see, e.g.*, page 15, lines 4-20, and page 10, lines 10-13); and 60/358,580 (*see, e.g.*, page 10, lines 7-10, and page 11, lines 1-4).

Support for amended claim 19 can be found at, *inter alia*, page 15, lines 8-30; page 24, lines 15-32; page 19, lines 27-29; page 20, lines 1-2; page 25, lines 1-15, and elsewhere in the specification as filed. Support is also found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/440,129 (*see, e.g.*, page 22, lines 25-30, and page 10, lines 13-17); and 60/358,580 (*see, e.g.*, page 10, lines 29-31).

Support for amended claim 20 can be found at, *inter alia*, page 15, lines 8-30; page 19, lines 27-29; page 20, lines 1-2; page 24, lines 15-32; page 25, lines 1-15; and elsewhere in the specification as filed. Support is also found in the priority documents, such as, for example, in U.S. Provisional

patent application Nos. 60/440,129 (*see, e.g.*, page 23, lines 15-20, and page 10, lines 13-17); and 60/358,580 (*see, e.g.*, page 10, lines 3-5).

Support for amended claim 21 can be found at, *inter alia*, page 15, lines 8-30; page 21, lines 27-29; page 24, lines 15-32; page 25, lines 1-15; page 142, lines 15-30; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 31, to page 11, lines 11); 60/440,129 (*see, e.g.*, page 24, lines 13-18); and 60/358,580 (*see, e.g.*, page 9, lines 24-33).

Support for amended claim 30 can be found at, *inter alia*, page 15, lines 20-30; page 24, lines 15-32; page 25, lines 1-15; page 31, lines 28-31; page 32, lines 1-15; page 142, lines 15-30; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 9, lines 5-13); 60/440,129 (*see, e.g.*, page 13, lines 16-25); and 60/358,580 (*see, e.g.*, page 9, lines 5-13).

Support for amended claim 35 can be found at, *inter alia*, page 59, lines 9-25; page 120, lines 3-11; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 18, lines 15-20); and 60/358,580 (*see, e.g.*, page 16, lines 30-31).

Support for new claim 36 can be found at, *inter alia*, page 15, lines 8-18; page 19, lines 24-27; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 10, lines 3-16); 60/440,129 (*see, e.g.*, page 15, lines 14-20, and page 10, lines 10-13); and 60/358,580 (*see, e.g.*, page 10, lines 7-9).

Support for new claim 37 can be found at, *inter alia*, page 15, lines 5-18; page 19, lines 27-29; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/440,129 (*see, e.g.*, page 25, lines 20-25; page 10, lines 13-17); and 60/358,580 (*see, e.g.*, page 10, lines 14-16).

Support for new claim 38 can be found at, *inter alia*, page 14, line 30, to page 15; page 20, lines 2-5; page 21, line 30, to page 22, line 2; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application Nos. 60/363,124 (*see, e.g.*, page 4, lines 9-11; page 9, lines 5-13); and 60/358,580 (*see, e.g.*, page 9, lines 9-10).

Support for new claim 39 can be found in the specification at, *inter alia*, page 14, lines 22-26; page 15, lines 3-19; page 20, lines 10-13; page 29, lines 25-31; and page 47, lines 27-31; and elsewhere in the specification as filed. Support can also be found in the priority documents, such as, for example, in U.S. Provisional patent application No. 60/363,124 (*see, e.g.*, page 4, lines 9-11; page 5, lines 13-22; and page 9, lines 5-13).

Amendments to the claims are made without prejudice or disclaimer, and do not constitute amendments to overcome any prior art or other statutory rejections and are fully supported by the specification as filed. Additionally, these amendments are not an admission regarding the patentability of subject matter of the canceled or amended claims and should not be so construed. Applicants reserve the right to pursue the subject matter of the previously filed claims in this or in any other appropriate patent application. The amendments add no new matter and Applicants respectfully request their entry.

The Sequence Listing

Applicants have enclosed a revised sequence listing and request its entry in place of the previously entered sequence listing. The new sequence listing includes a replacement sequence for SEQ ID NO:1905. The sequence represented as SEQ ID NO:1905 is identical to the sequence represented as GenBank entry NM_000484 (*see* page 153 of the present specification). The version of NM_000484 appearing in the sequence listing as SEQ ID NO:1905 appeared in GenBank on October 31, 2000, and is included in the priority application, U.S. Provisional patent application No. 60/363,124 (*see* page 425 of 60/363,124). The revised sequence listing adds no new matter and Applicants respectfully request its entry.

Information Disclosure Statements

The Office declined to consider European application no. 1144623 B1, cited in the Information Disclosure Statement dated December 8, 2006, for allegedly wanting an English language translation. An English language abstract of the European patent application is enclosed, together with a substitute page 6 of the PTO 1449 form, listing the English language abstract of European patent application. The Applicants request the Examiner's consideration of that abstract and execution of the enclosed substitute PTO 1449 form page.

Furthermore, the Office considered only the abstracts for International patent publication WO 01/42443, WO 01/70944, WO 02/55692, and WO 02/55693, and not the complete reference because

full copies were allegedly not provided. Since the original international publication documents are in a foreign language and no English language translations are available, consideration and entry of the English language abstracts of those documents is acceptable.

Priority

The Office has acknowledged a priority date of March 11, 2002, based on U.S. provisional application no. 60/363,124, but alleged that there is no support in U.S. Provisional application no. 60/358,580, filed February 20, 2002, for a chemically modified double stranded siRNA comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) comprising SEQ ID NO:1905 as presently claimed. The Examiner also alleges that "Provisional Application 60/358,580 does not appear to have support for a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to human amyloid precursor protein (APP) RNA comprising SEQ ID NO: 1905 as instantly claimed." Office Action, at page 5. Applicants respectfully traverse, but because an earlier priority date is not required to obviate the outstanding rejections, the applicants forgo detailed arguments here but reserve the right to demonstrate entitlement to an earlier priority date should the necessity arise.

The Office has also requested an update of the applications listed in the priority claim. As of today, and to Applicants' knowledge, all of the pending U.S. utility applications listed in the priority claim remain pending.

Objection under 35 USC § 132(a)

The amendment filed March 10, 2007, was objected to under 35 U.S.C. § 132(a) for allegedly introducing new matter by way of a new sequence listing submission in which SEQ ID NO:1905 has been added. Specifically, the Office alleged that the inclusion of uracil residues in SEQ ID NO:1905 in lieu of thymine residues in the sequence for GenBank entry NM_000484 constitutes new matter. Applicants have submitted a revised sequence listing with a revised SEQ ID NO:1905 to replace an earlier sequence listing filed on March 10, 2007. The sequence in SEQ ID NO:1905 contained in the revised sequence listing submitted herewith is the same as the sequence for GenBank entry NM_000484. Accordingly, the objection is now moot. Withdrawal of the objection is in order and is respectfully requested.

Rejection under 35 USC § 112, first paragraph

Claims 1-3, 14-21, 30, and 35 were rejected under 35 U.S.C. §112, first paragraph, for failure to comply with the written description requirement. Specifically, the Office alleged that the instant specification does not support SEQ ID NO:1905, which was added to the sequence listing in the amendment filed on March 10, 2007, in that the inclusion of uracil residues in SEQ ID NO:1905 in lieu of thymine residues found in the sequence of GenBank entry NM_000484 has no support in the instant specification. The Office believes that the introduction of SEQ ID NO:1905 constitutes new matter. In light of the revised sequence listing submission herein, the rejection is moot. Withdrawal of 35 U.S.C. §112, first paragraph, rejection against the pending claims is in order and is respectfully requested.

Rejections under 35 U.S.C. § 103(a)

Claims 1-3, 4-21, 30, and 35 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over GenBank Accession No. NM_000484 in view of Coulson et al (Brain Research, 1997, Vol. 770:72-80); Elbashir et al. (2001, *The EMBO Journal*, Vol. 20, No. 23, pages 6877); Matulic-Adamic et al. (U.S. Patent No. 5,998,203); and/or Parrish et al. (2000, *Molecular Cell*, Vol. 6, p. 1077-1087). Applicants respectfully traverse this rejection.

The Office relies on GenBank Accession Number NM_000484 (“GenBank”) as the primary reference for allegedly teaching the sequence of human amyloid precursor protein (APP) gene. However, the Office acknowledged that GenBank does not teach any chemically modified siNA comprising a sense strand and antisense strand as presently claimed. Furthermore, GenBank is completely silent with respect to any siNA, let alone chemically modified siNA. Just like the disclosure of a gene sequence associated with a disease state does not render a subsequently discovered inhibitor (chemical or biological) obvious, mere disclosure of the APP gene sequence is not a teaching or suggestion of chemically modified siNA. The connection is simply too tenuous.

Coulson, Elbashir, Matulic-Adamic, and Parrish, alone or in combination, do not cure the deficiencies due to what GenBank Accession Number NM_000484 does not teach. The Office relies on Coulson as a secondary reference for allegedly teaching that "amyloid precursor protein mediates a substrate-specific interaction between neurons and extracellular matrix components," and that "**antisense oligonucleotides** targeted to the amyloid precursor protein affects adhesion of dorsal root ganglia neurons." Office Action, at page 10. The Office also stated that "Coulson et al. ... teaches the

desire to modulate the levels and metabolism of amyloid precursor protein as a possible therapy for Alzheimer's disease." However, it is clear that Coulson teaches only the treatment of murine neurons using antisense oligonucleotides. *See Coulson, Abstract* ("Primary cultures of murine neurons were treated with antisense oligonucleotides to down-regulate APP."). Indeed, the Office acknowledged that Coulson does not teach any chemically modified siRNA comprising a sense strand and antisense strand as presently claimed. *See Office Action*, at page 10. Furthermore, for reasons discussed in more detail below, antisense art is non-analogous to the art in which the presently claimed invention is encompassed. At the time of the priority date, although little was known about the specific mechanism of the action of siRNAs, those of ordinary skill in the art did know that the antisense molecules and siRNAs functioned in very different ways, and therefore would have anticipated that different structural features of nucleic acids would have been required for their activities. Thus, it is improper to premise an obviousness rejection on Coulson.

The Office relies on Elbashir as the secondary reference for allegedly teaching siRNA molecules and 2'-O-methyl and 2'-deoxy modifications to dsRNA molecules. However, in the section entitled "*2'-deoxy- and 2'-O-methyl-modified siRNA duplexes*" (*see, pages 6881-6882*), Elbashir describes the effect of chemical modification on the activity of the siRNA duplex to mediate RNAi. The authors state, on page 6881 (bottom of the right hand column) that:

To assess the importance of the siRNA ribose residues for RNAi, duplexes with 21 nt siRNAs and 2 nt 3'-overhangs with 2'-deoxy- or 2'-O-methyl-modified strands were examined (Figure 4). Substitution of the 2 nt 3'-overhangs by 2'-deoxynucleotides had no effect and even the replacement of two additional ribonucleotides by 2'-deoxynucleotides adjacent to the overhangs in the paired region produced significantly active siRNAs. Thus, 8 out of 42 nt of a siRNA duplex were replaced by DNA residues without loss of activity.

Thus, while 2'-deoxy substitutions at the 3'-terminal positions were permitted, there was no mention of any active siRNAs using 2'-O-methyl modifications, even at the terminal positions. Furthermore, because complete substitution of one or both siRNA strands with either 2'-deoxy or 2'-O-methyl residues resulted in a complete loss of RNAi activity (*see, e.g., Abstract*), the results of Elbashir suggests that modification of internal nucleotides positions reduced the ability of siRNAs to mediate RNAi, probably by interfering with protein interactions or siRNA assembly. Thus, Elbashir does not teach or suggest a chemically modified nucleic acid molecule comprising sense and sense strands, each stand having about 50 to 100% of its nucleotides chemically modified. Furthermore, Elbashir does not teach or suggest a chemically modified nucleic acid molecule comprising a structure

where the antisense strand comprises a nucleotide sequence of 18 to 27 nucleotides that is complementary to a human APP RNA encoded by SEQ ID NO:1905.

The Office acknowledges that "[i]t is noted that complete substitution of one or both siRNA strands by 2'-deoxy residues or by 2'-O-methyl residues abolished RNAi activity," but stated that "the instant claims do not recite any functional language, therefore, the skilled artisan would have been motivated to incorporate such substitution/chemical modifications to a siRNA molecule as discussed below." Office Action, at page 11. Applicants respectfully point out that this statement does not come close to explain why the skilled artisan would be motivated to make modifications that he knew for certain would not work. Indeed, Applicants believe that the instant obviousness rejection is improperly premised upon hindsight as evidenced by this statement. Regardless of whether Applicants use functional language in their claims, as the motivation to combine and modify prior art references should come from the references themselves and what was known in the art at the time of filing, and not the application at issue, a skilled artisan tend to rely on the teachings in the art so as to avoid the known pitfalls. Applicants submit that Elbashir expressly teaches known pitfalls such as those concerning the complete substitution of 2'-deoxy residues and/or any substation of 2'-O-methyl residues. Accordingly, the Elbashir reference teaches away from the present invention and could not have rendered the instant claims obvious, and the Office should not rely on Applicants' own teachings for its finding of obviousness.

Matulic-Adamic is relied on as a secondary reference for allegedly teaching a terminal cap moiety at the 5'-end, 3'-end or both ends, including an inverted deoxyabasic moiety. However, Matulic-Adamic teaches chemical modification of **ribozymes**. For the reasons discussed in more details below, ribozyme art is non-analogous art to the claimed invention. At the time of the priority date, although very little is known about the mechanism of action of siRNAs, those of ordinary skill in the art did know that ribozymes function in very different ways from siRNAs, and accordingly could be expected to require different structural features for activity. Thus the Office should not have relied upon Matulic-Adamic as a basis for an obviousness rejection in this case.

Parrish is relied upon as a secondary reference for its alleged teachings concerning chemically modified double stranded siRNA molecules having 2-deoxy-2'-fluoro pyrimidine modifications in the sense or antisense strand. Applicants respectfully submit that this reading of Parrish is superficial and problematic, and that a more exact reading of Parrish would indicate it to be an unsuitable reference on which to base an obviousness rejection. Specifically, Parrish does not teach or suggest the claim limitation that "each strand of the nucleic acid molecule is independently 18 to 27 nucleotides in

length," because it only teaches chemically modified long (about 742 nts) RNAs. *See* Parrish, at page 1081, left column, in the text accompanying Figure 5 ("2'-fluorouracil, 2'-aminouracil, 2'-deoxythymidine, and 2'-deoxy-cytidine were incorporated into individual strands of the 742 nt unc-22A segments using T3 and T7 polymerases (Experimental Procedures)" (*emphasis added*)). Further, Parrish does not teach the claim limitation that "one or more of the purine nucleotides present in one or both strands of the nucleic acid molecule are 2'-O-methyl purine nucleotides and one or more of the pyrimidine nucleotides present in one or both strands of the nucleic acid molecule are 2'-deoxy-2'-fluoro pyrimidine nucleotides." To the contrary, Parrish describes 2'-deoxy-2'-fluoro uridine modifications but not 2'-deoxy-2'-fluoro cytidine modifications. Indeed, Parrish describes that 2'-deoxy cytidine is not tolerated and would therefore lead those skilled in the art to conclude that 2'-deoxy-2'-fluoro cytidine would not be tolerated. *See* Parrish, at page 1081, right column ("Modification of cytidine to deoxycytidine ... on either the sense or the antisense strand of the trigger was sufficient to produce a substantial decrease in interference activity."). Therefore, Parrish cannot be relied upon for teaching or suggesting the use of 2'-deoxy-2'-fluoro pyrimidine modifications, which encompasses both 2'-deoxy-2'-fluoro uridine and 2'-deoxy-2'-fluoro cytidine substitutions. Also Parrish describes 2'-deoxy-2'-fluoro modification of uridine in either the sense strand or the antisense strand, but never simultaneously in both strands, as was first taught by Applicants and as is presently claimed as an embodiment to claim 1 herein. *See, e.g.*, Parrish, at page 1081, left column, Figure 5B (describing that interference activities of unc-22 were retained with a uracil → 2'-fluorouracil in the sense strand, and unmodified RNA antisense strand; or with an unmodified RNA sense strand and a modified, uracil → 2'-fluorouracil antisense strand). Thus Parrish does not remedy the gap of disclosure left by the other cited references.

The Office argues that it "would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make a chemically modified double stranded short interfering nucleic acid (siNA) molecule comprising a sense strand and an antisense strand, wherein the antisense strand is complementary to a human amyloid precursor protein (APP) RNA comprising SEQ ID NO: 1905 using the sequence taught by GenBank ..., the motivation of Coulson..., and following the methods of Elbashir..., Matulic-Adamic ... and Parrish...." The Office argued that it would have been obvious to one skilled in the art to incorporate certain modifications into one or both strands of siNA such as 2'-O-methyl purines and 2'-deoxy-2'-fluoro pyrimidine nucleotides as allegedly taught by Elbashir; a terminal cap moiety on one end of the sense strand as allegedly taught by Matulic-Adamic; and phosphorothioate internucleotide linkage at the '3 antisense end or a terminal

phosphate at the 5' antisense end as allegedly taught by Elbashir. The Office argues that one would have been motivated to make such a chemically modified molecule having sense and antisense strands, wherein the antisense strand is complementary to APP RNA comprising SEQ ID NO:1905 for use in Alzheimer's disease therapy because of Coulson's alleged teachings concerning the use of antisense oligonucleotides in down-regulating the APP expression. The Office further argues that one would have been motivated to include chemical modifications such as 2'-O-methyl or 2'-deoxy-2'-fluoro pyrimidine modifications because Elbashir, Matulic-Adamic, and Parrish allegedly taught the use of such modifications to confer benefits to double stranded nucleic acids. The Office finally argues that one skilled in the art would also have a reasonable expectation of success because chemical modifications of double stranded siRNA molecules are well-known to one skilled in the art and that combinations of such modifications are merely a design choice.

Under 35 U.S.C. § 103(a), to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the references, when combined must teach or suggest all the claim limitations. *See* MPEP 2143. Applicants take the position that the Office has failed to establish a *prima facie* case of obviousness.

As explained above, none of the cited references, alone or in combination, render obvious the presently claimed nucleic acid molecules because the cited references do not teach or suggest all of the claim elements. Applicants further disagree with the Office's allegation that it would have been obvious to make short double stranded nucleic acid molecules having chemical modifications with a reasonable expectation of success merely because chemical modification of oligonucleotides were known in the art and would be expected to impart benefits to siRNA because such modifications had been shown to benefit antisense oligonucleotides, ribozymes, and long dsRNAs.

Initially, Applicants submit that antisense art, ribozyme art, and long dsRNA art are not analogous art to the siRNA technology, which encompasses the presently claimed invention, and should not be the basis for an obviousness rejection. Any reference or general knowledge cited to demonstrate obviousness must be analogous art. The reference must either be in the field of Applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned." *In re Oetiker*, 977 F.2d 1443, 1447 (Fed. Cir. 1992).

Specifically, antisense art, ribozyme art, and long dsRNA art are not reasonably pertinent to chemically modified siRNA molecules that target APP RNA. Antisense molecules are substantially

single-stranded prior to interacting with their target, while siRNA is almost completely in a duplex form; it is well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Antisense molecules will tolerate substantial 5' and 3' terminal modifications; in contrast, the activities of siRNAs are almost completely destroyed by attaching modifications to the 5' end of the antisense strand of the siRNA. The activity of an antisense molecule is destroyed by modifications that alter the DNA-like structure at the core of molecule. It was not clear in 2001 whether the siRNA duplex would need to maintain an RNA-like structure or whether other structures would be permitted.

Likewise, ribozymes fall within a non-analogous art. Like antisense molecules, ribozymes are substantially single-stranded prior to interacting with their target, while siRNAs are almost completely in duplex form. As explained above, it is well known to those skilled in the art that single-stranded nucleic acid is more susceptible to nuclease attack than is double-stranded nucleic acid. Additionally, ribozymes are known to tolerate substantial 5' and 3' terminal modifications. In contrast, the activity of siRNA molecules is almost completely abolished by attaching modifications to the 5' end of the antisense strand of the siRNA. Also, unlike siRNA molecules, ribozymes must form a complex RNA secondary structure before becoming active.

Finally, long dsRNAs fall squarely outside the siRNA technology. As discussed above, Elbashir attempted to apply chemical modifications to siRNA based on the teachings of the prior art, for example, Parrish, but failed beyond replacing 3'-terminal ribonucleotides with deoxynucleotides. Those molecules were found to have significantly diminished activity or were totally inactive in inducing target specific cleavage by RNAi. Figure 4 of Elbashir clearly shows that only limited 2'-deoxy substitutions at the 3'-end of a siRNA molecule could be tolerated. Furthermore, 2'-O-methyl substitutions were shown to be not tolerated for RNAi in all cases. Therefore, the 2'-deoxy modification, which Parrish had found to be tolerated in long dsRNAs (see, Parrish, page 1081 and Figure 5), was found by Elbashir to be not tolerated in short double stranded RNAs. This comparison clearly would have suggested to those skilled in the art that short double stranded RNA molecules are not amendable to the same types of chemical modifications that may be used to modify long dsRNAs without resulting in diminished RNAi activity.

At the priority date of the present application, while little was known about siRNAs, those of ordinary skill in the art did understand that siRNAs function in a very different way from antisense nucleotides, ribozymes, and long dsRNAs. Because of these differences in mechanisms, those of ordinary skill in the art would have anticipated that different structural features would be required for

activities in siRNA versus long dsRNAs, ribozymes, and/or antisense nucleotides. Accordingly, they had no basis of predicting the effect of various types and positions of chemical modifications on the activity of a double stranded nucleic acid molecule as claimed herein, let alone the expectation of success.

For the reasons discussed above, the cited references, alone or in combination, do not render obvious the instantly claimed methods of synthesizing chemically modified nucleic acid molecules. Accordingly, withdrawal of the 35 USC §103(a) rejection of the claims based on GenBank, Coulson Elbashir, Matulic-Adamic and/or Parrish is in order and is respectfully requested.

In view of the foregoing amendments and remarks, Applicants submit that the claims are in condition for allowance, which is respectfully solicited. If the Examiner believes a teleconference will advance prosecution, she is encouraged to contact the undersigned at the telephone number below.

Respectfully submitted,



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